PATENT
Docket No. 432722002612

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Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Gregory R. Mundy, *et al.*

Serial No.: 10/052,832

Filing Date: January 15, 2002

For: INHIBITORS OF PROTEASOMAL ACTIVITY FOR STIMULATING HAIR GROWTH (AS AMENDED)

Examiner: R.J. Gitomer

Group Art Unit: 1627

DECLARATION OF GREGORY R. MUNDY PURSUANT TO 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Gregory R. Mundy, declare as follows:

1. I am one of the co-inventors of the subject matter claimed in the above-referenced application.

2. Other co-inventors and I have conducted experiments demonstrating that pentoxifylline (PTX) is not a proteasomal inhibitor. The experimental results demonstrating the lack of proteasomal activity by PTX are set forth in the following paragraphs and in the attached Figure 1.

Application Serial No.	Filing Date	Status
09/113,947	July 10, 1998	☒Patented ☐Pending ☐Abandoned
09/361,775	July 27, 1999	☒Patented ☐Pending ☐Abandoned
09/421,545	October 20, 1999	☐Patented ☒Pending ☐Abandoned
09/695,807	October 23, 2000	☐Patented ☒Pending ☐Abandoned

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

12/19/03
Date

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12/19/03
Date

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sd-176692

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SUBSTITUTE DECLARATION FOR UTILITY PATENT APPLICATION

AS BELOW-NAMED INVENTORS, WE HEREBY DECLARE THAT:

Our residences, post office addresses, and citizenship are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled: INHIBITORS OF PROTEASOMAL ACTIVITY FOR STIMULATING BONE AND HAIR GROWTH, the specification of which is attached hereto unless the following box is checked:

☒ was filed on January 15, 2002 as United States Application Serial No. 10/052,832 and was amended on July 29, 2002, May 22, 2003, and November 3, 2003.

WE HEREBY STATE THAT WE HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

We acknowledge the duty to disclose information which is material to the patentability as defined in 37 C.F.R. § 1.56.

We hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed:

Application No.	Country	Date of Filing	Priority Claimed?
			☐Yes ☐No

We hereby claim benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date

We hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, we acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

3. Proteasomal activity was determined using the assays described in the instant specification. *See* specification, at page 17, lines 8-20 and Example 5. Briefly, the effects of inhibitors of proteasomal activity were assessed using a fluorogenic peptide chymotryptic substrate. The 20S proteasomes from the methanoarchaeon *Methanosarcina thermophila* produced in *E. coli* and the substrate Suc-Leu-Leu-Val-Tyr-AMC were obtained from Calbiochem-Novabiochem Corp. Briefly, serial dilutions of the inhibitor to be tested were mixed with proteasome solution at a proteasome concentration of 0.01 mg/ml. After 30 minutes of incubation at 37°C, substrate solution at a final concentration of 20-30 μg/ml was added; the mixture was incubated at 37°C and then read at 15, 30, and 60 minutes in a Titertek Fluoroskan II (MTX Lab Systems, Inc., Vienna, Virginia, USA). Five different compounds were tested using increasing concentrations of each compound.

4. Figure 1 shows the results the inhibitory activity of several compounds in the proteasomal activity assay performed as described in paragraph 3. MG262, PS1, and MG132 inhibited proteasomal activity as evidenced by the decreasing amount of fluorescence detected as the concentration of the test compound increased. Maximal inhibition occured for MG262 at 1μM, for PS1 at 10 μM, and for MG132 at about 50 μM. However, the NF-κB inhibitors, α-benzoylamino-1,4-naphthoquinone (PPM18) and pentoxyfilline (PTX), failed to inhibit proteasomal activity. Thus, our data demonstrates that PTX fails to inhibit proteasomal activity.

5. To my knowledge, there has been only one report identifying PTX as a proteasomal inhibitor. The report identifying PTX as a proteasomal inhibitor is Combaret et al., *Mol. Biol. Rep.* 26:95-101 (1999). This reference is cited in the original disclosure as filed at page 29, lines 17-20 as it was published prior to the submission of the application. However, based on our testing of PTX, I do not believe that Combaret report is accurate.

6. The other publications I have reviewed regarding the functional activity of PTX do not identify PTX as a proteasomal inhibitor. PTX is alternatively classified as a NF-κB inhibitor or a phosphodiesterase inhibitor. For example, Chen et al. discussed the action of PTX on TNF-a mediated activity in vascular smooth muscle cells. *See* Exhibit A. In their discussion

on pages 954-956, the various activities of PTX were disclosed only as NF-κB inhibition and phosphodiesterase inhibition. Likewise in Lee et al. disclosed PTX as having only two identified inhibitory functions - the inhibition of NF-κB activity and of phosphodiesterase activity. *See* Exhibit B at, *e.g.*, Abstract.

7. In view of our own data demonstrating that PTX fails to inhibit proteasomal activity and the inability of other skilled artisans to reproduce the observations reported by Combaret, I do not believe that PTX is a proteasomal inhibitor.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to by true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Executed at San Antonio, Texas, on March 7th, 2004.

Gregory R. Mundy